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# Purpura Arthralgia Weakness Mixed Cryoglobulinemia Syndrome Treated with Splenectomy

## A Case Report

**Carl R. Haeger, MD***

*Weakness purpura mixed arthralgia cryoglobinemia (IgG - IgM) syndrome was first described by Meltzer in 1966. Such a case was recently reported after treatment with Cyclophosphamide and subsequent splenectomy for pancytopenia with beneficial effects on the cryocrit. The patient reported here underwent splenectomy without Cyclophosphamide and had subsequent amelioration of the clinical symptoms. Abnormal plasma cells found in the spleen presumably were responsible (at least in part) for the patient's symptomatology.*

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THE arthralgia, purpura weakness mixed cryoglobinemia syndrome with rheumatoid factor activity has been reported by Meltzer [1,2] and others. [1-10] Mathison has reported the beneficial effects of Cyclophosphamide and incidental splenectomy in one patient with this syndrome.[3] Our report is of a patient with this syndrome treated with splenectomy without Cyclosphosphamide. Subsequently, our patient had amelioration of symptoms without fall in cryocrit. The spleen was enlarged weighing 247 gms and filled with abnormal cells presumably manufacturing the IgM component of the cryoglobulin.

### Case Summary

This 39-year-old beautician was first referred to Henry Ford Hospital in January, 1970 with a three-year history of purpuric lesions appearing intermittently on her legs (Figure 1). These were associated also with urticaria. The purpuric lesions were heralded by a burning, stinging pain. They began as small red lesions with a surrounding halo and over a period of days gradually became brownish and macular. The patient had also experienced several months of foot drop with paresthesia in her right leg. This cleared spontaneously. She also complained of generalized intermittent joint pain although joint swelling was never clearly evident. Past history included a total hysterectomy with bilateral salpingo-oophorectomy in 1952 because of excessive vaginal hemorrhage. Postoperative diagnosis was periuterine pel-

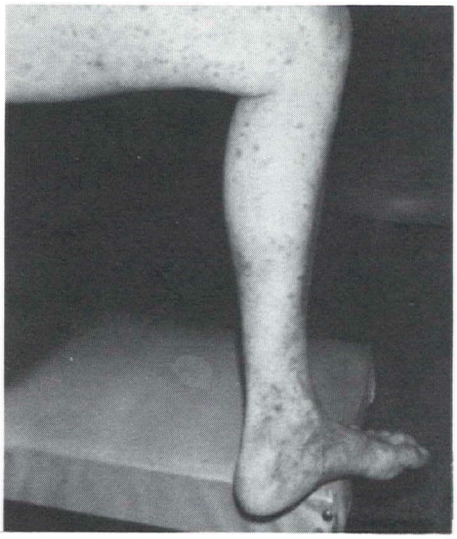
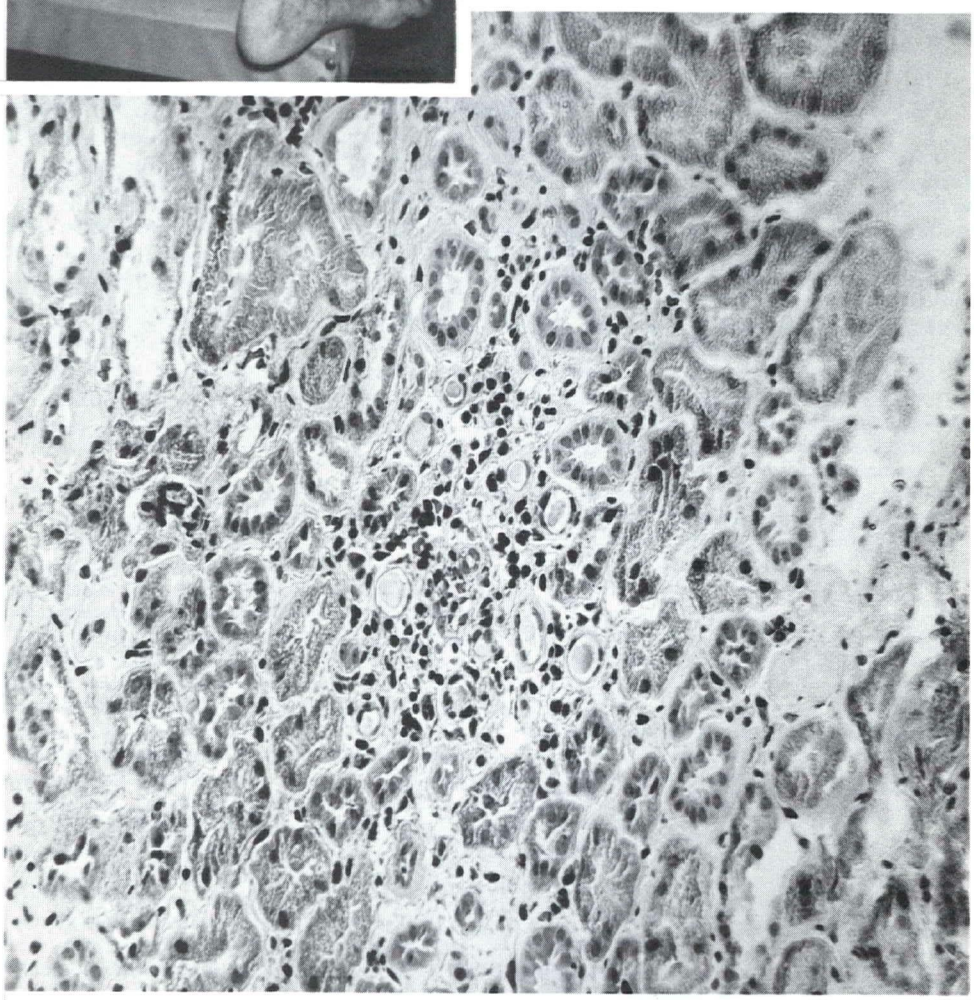


**Figure 1**
**Patient's leg showing typical purpuric lesions.**

**Figure 2**
**Section of kidney showing interstitial infiltration with mononuclear cells.(High power, 300 x H& E)**



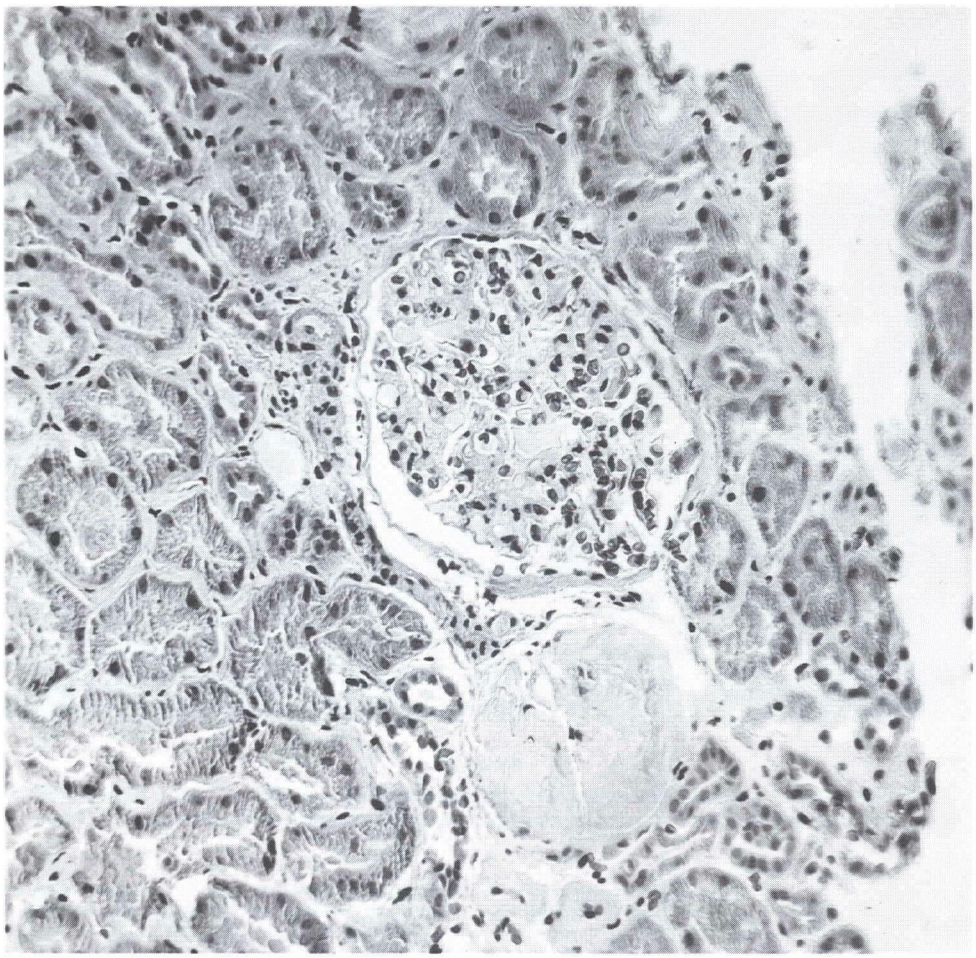


**Figure 3**
**Kidney biopsy of patient showing prominent glomerular hyalinization. Mesangial thickening is also present.**

vic adhesions, fibro-cystic cervicitis, bilateral salpingitis with ovarian cysts. For a period of time she received thyroid medication. When it and estrogen therapy were discontinued in 1969, there were no untoward results. The patient also complained of severe retro-orbital headaches. The main physical findings were purpuric lesions of the legs and hyperpigmentary changes of the legs.

Initial evaluation revealed mixed cryoglobulins of the IgG-IgM variety and a titer 5 volumes %. Rheumatoid factor activity was elevated at 1 to 620. The differential rheumatoid agglutination test of 40 at time of examination rose to 1240 in the next two years.

When she was admitted to Henry Ford Hospital in 1972, diagnostic gastrointestinal tests and IVP were negative except for a finding of a 5 mm polyp in the cecal tip. IgG was elevated at 1674 mg/ml and IgA was elevated at 390. White blood count was 6.2x103, hemoglobin 14.8, hematocrit 42.1 and mean corpuscle volume 93. Cryglobulins at that time were 5 volumes percent. Kidney biopsy showed chronic focal interstitial nephritis

**Figure 4**

**Glomerulus. Very abnormal. Thickened basement membranes, possible electron dense deposits in the basement membrane. Foot processes touching mitochondria vastly altered. X 12,000.**

(Figure 2). However, glomerular hyalinization was prominent (Figure 3). Electron microscopy showed evidence of basement membrane thickening of capillaries (Figures 4 and 5). Serum complement was 63 GH50/ml. Creatinine clearance was 94 ml/min. There was no evidence of hematuria. The patient obtained partial relief with Benadryl, Atarax and support stockings; but she was virtually incapacitated by disabling pain and swelling in her legs.

Elective splenectomy was done in March of 1972. The postoperative course was uneventful. One month later the patient reported that her purpuric lesions were much less noticeable and new lesions were few and less apt to be associated with pain or swelling. The headaches had disappeared and joint symptoms were minimal.

In late summer, symptoms began to increase but were less than before splenectomy. Anticoagulant therapy was initiated, again with a noticeable decrease in symptoms.

## Discussion

Proteins that reversibly precipitate from blood on cooling were first described by Wintrobe and Buell[11] in 1933 and first named cryoglobulins by Lerner and Watson in 1947.[12] They are most commonly encountered in multiple myeloma, macroglobulinemia, and malignant lymphomas but occur rarely in cirrhosis, sarcoidosis, subacute bacterial endocarditis, leprosy, syphilis, infectious mononucleosis, cytomegalo virus disease, various connective tissue disorders, and in so-called "essential cryoglobulinemia." Most of these proteins are immunoglobulins although

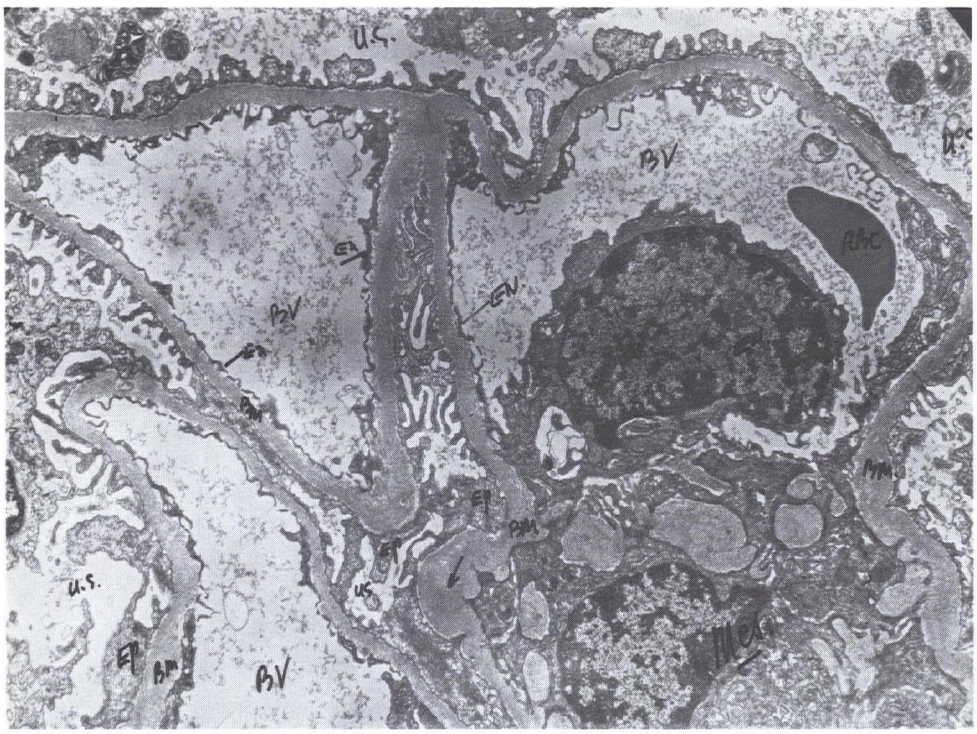



**Figure 5**

**Same changes as Figure 3. However, to much lesser degree with areas of normal glomerulus. X 12,000.**

cryofibrinogens have also been found. In most instances, these cold precipitating proteins are an incidental finding, but they can give rise to symptoms of severe vascular insufficiency usually involving the extremities. The pathophysiology of the vasculitis is not well understood but is thought to be an autoimmune phenomenon. In 1966, Meltzer and Franklin reviewed 29 patients with cryoglobulinemia and found they could divide the patients into three groups.[2] The first group had IgG (7S) gammaglobulins. These patients clinically had multiple myeloma, cancer, essential cryoglobulinemia and cirrhosis and had negative rheumatoid factors. One half were symptomatic and most were monoclonal with either K or L chains. Group II patients had IgM (19S) gammaglobulins. Clinically, these patients had leukemia and lymphosarcoma and a negative rheumatoid factor. This group tended to be monoclonal with either K or L chains and asymptomatic.

As in our case, their group III patients had mixed IgG-IgM gammaglobulins and were predominantly female. All the serums contained rheumatoid factors, usually IgG-IgM in type although one was a polymer of IgG. The cryoprecipitate tended to be polyclonal with both K and L chains, although this may be due to the fact that there are two immunoglobulins (IgM acting as antibody and altered IgG as antigen). All these patients were symptomatic and most had an unusual but easily recog-

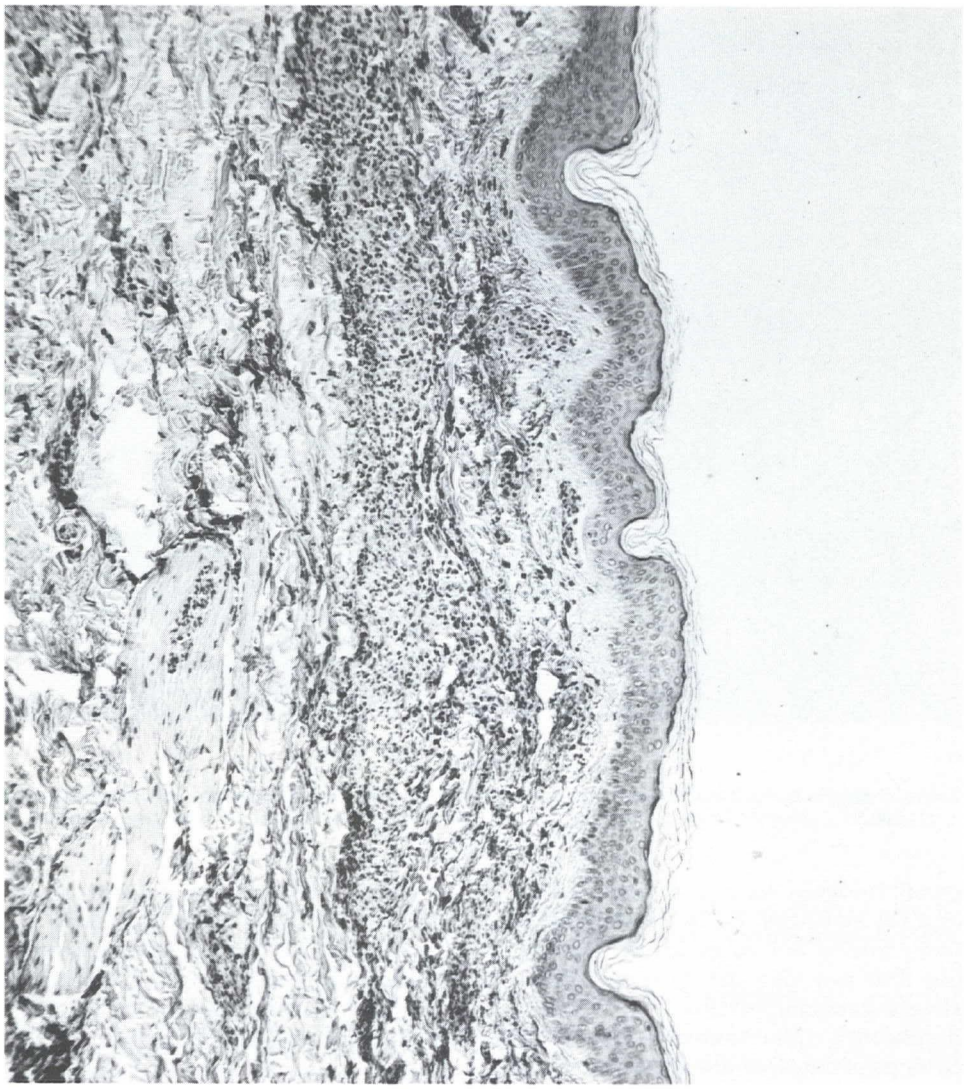


**Figure 6**
**Low power view of skin; showing perivascular inflammatory cell infiltrate. 115x**

nized clinical picture composed of weakness, purpura, arthralgia and elevated rheumatoid factor activity.

The patients with purpura had burning, stinging pain which was relieved partially by antihistamines. Lymphadenopathy, hepatosplenomegaly, epistaxis, uveitis, parotid swelling, and neuritis have all been reported in the mixed type of cryoglobulinemia. [4-9] Furthermore, underlying malignancy or other disease were not found. It is noteworthy that the arthralgias were unaccompanied by swelling and redness. Two of the patients had Sjogren's syndrome, and one had thyroiditis, presumably of the

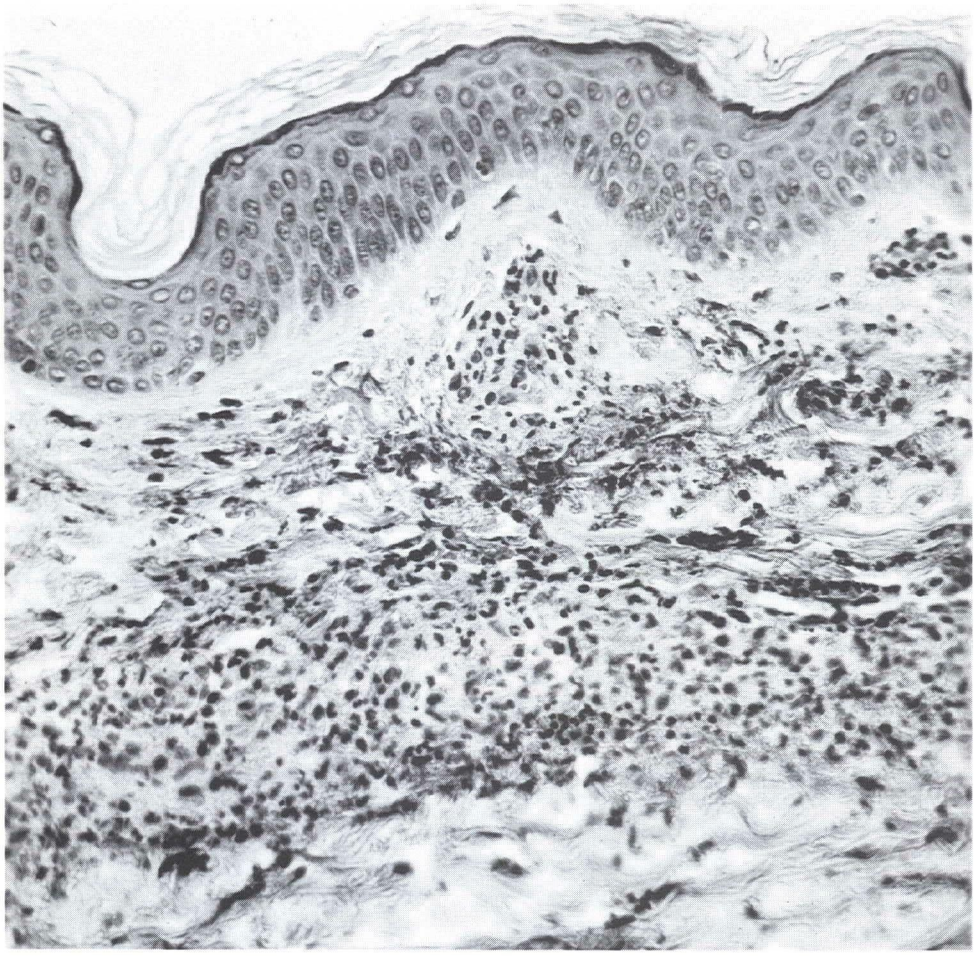


**Figure 7**

**Higher magnification of the skin showing infiltration with occlusion of the lumen in some small vessels. 300x H & E stain.**

autoimmune type. The occurrence of nephritis rapidly progressed to acute renal failure, which has been reported in other series also.[10]

Hemolytic anemia, renal tubular acidosis, and thrombocytopenic purpura have been reported. [2,4,7] The rheumatoid factor seems to have different physical properties than classic rheumatoid factor. Serum complement was low, especially in patients with glomerular lesions. They had either a normal serum protein electrophoresis or a diffuse hypergammaglobulinemia rather than a monoclonal spike. Rheumatoid factor was generally quite elevated. Three patients studied at autopsy had findings of diffuse glomerulonephritis, arteritis and endocarditis.

Small vessels in the dermis showed infiltration of the walls and surrounding tissue with neutrophils and a smaller number of mononuclear cells. No

intraluminal precipitate or necrosis were seen. The lesions were similar to those seen in Henoch-Schonlein purpura. Figure 1 is a photograph showing the skin of our patient. Figures 6 and 7 are photomicrographs of the skin section showing infiltration with occlusion of the lumen in some small vessels.

The glomerular lesions were characterized by swelling and proliferation of endothelial and axial cells, mild to moderate neutrophil infiltration and slight increase in basement membrane-like material generally seen in axial regions[2] (See Figure 3). Immune deposits in glomeruli and electron dense glomerular endothelial deposits have been reported by means of electron microscopy and immunofluorescence.[3] A section of our patient's kidney (Figure 2) shows capsular thickening and hyalinazation and mild proliferative changes (Figure 3). Endocarditis was found in one patient with a focus of necrosis and leukocyte infiltration. Inflammation could be seen in the small vessels at the base of the mitral valve.[2] The valvular lesion did not have the appearance of atypical verrucous endocarditis.

It is supposed that for the kidney — the circulating complexes fix complement and cause glomerular basement membrane damage similar to the glomerulonephritis or systemic lupus erythematosis. In the skin — the complexes may precipitate in the cooler surface areas and cause intravascular coagulation and vasculitis damage in some way.

The red blood cells adsorb complexes and with the fixation of complement, hemolysis occurs. The red blood cell is the "innocent bystander." There must be other factors present however, because this type of vascular damage was not seen with patients with rheumatoid arthritis and high circulating rheumatoid factor. Also, patients with multiple myeloma and lymphoma do not have this type of vasculitis in spite of higher levels of circulating cryoglobulins. In fact, the IgG-IgM complexes may be a by-product rather than a cause of the disease.

Other possible clinical expressions of immune complex disorders include synovitis, serositis, hyperviscosity syndromes, Raynaud's phenomenon, leukopenia and thrombocytopenia.

Many therapies have been tried for this disease. Elastic stockings, elevation of legs and avoidance of cold reduce but do not eliminate the patient's symptoms. Salicylates may be helpful for the control of arthralgias.

The burning, stinging pain of the purpura which may reflect the initial advent of vasculitis is helped by antihistamines, especially Atarax. Anticoagulant therapy has been used with dramatic benefit in two patients with leg ulcers.[13,14] Although the use of steroids seems logical because of their anti-inflammatory effects, they are usually of no benefit. Likewise, sympathectomy has not been of benefit. Penicillamine has been of benefit in some patients working perhaps by causing disruption of disulpide linkages of macroglobulins or by acting as a cytotoxic agent.[4] Chlorambucil and steriods have also been used without much benefit.[15,16] Cyclophosphamide, however, appears to lower the cryocrit and ameliorate the clinical symptoms. In one patient who developed pancytopenia while taking Cyclophosphamide, splenectomy was done in the hopes that Cyclophosphamide could be restarted since hypersplenism was suspected. After splenectomy, the cryocrit fell and hematuria and skin lesions abated.[3] Our patient underwent splenectomy without previous Cyclophosphamide and had good relief of symptoms. Slight exacer-

**Figure 8**
**Low power view of our patient's spleen. 115x. H & E stain.**

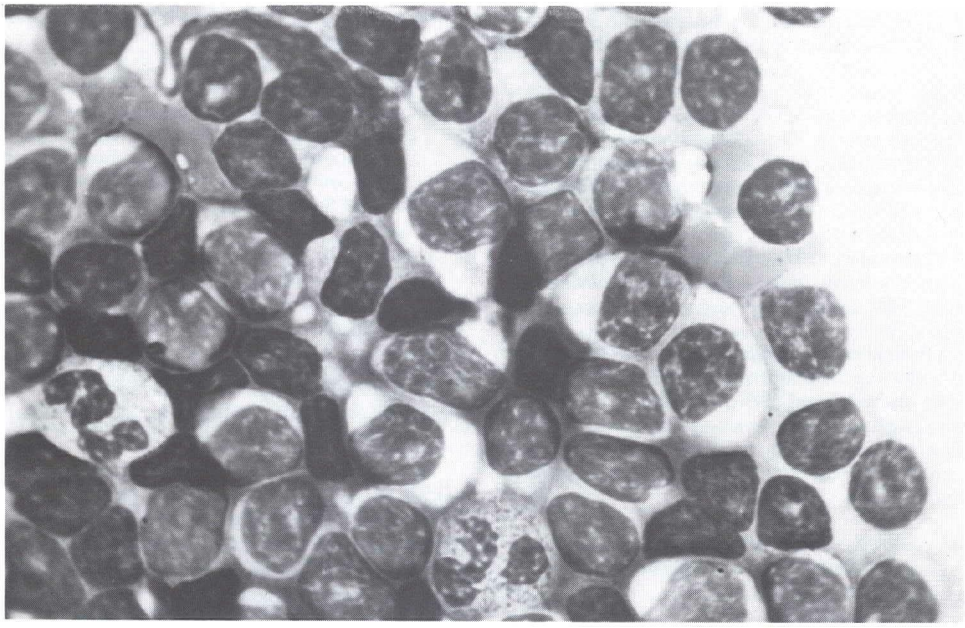


**Figure 9**
**High power view showing atypical plasmacytoid lymphocytes. 300x. Wright's imprint.**

bation was noted six months post-splenectomy and anticoagulants were begun again, with relief of symptoms. We feel splenectomy should be considered in patients with this disease.

Figures 8 and 9 show photomicrographs of our patient's spleen. Although the low power view is relatively normal, the high power view shows atypical plasmacytoid lymphocytes. Presumably these cells are manufacturing the IgM antibody versus the altered IgG. We cannot explain why the cryocrit seemed to rise as the patient improved, but since the pathophysiology of this disease is not clearly understood, we feel the latter effect is more important.

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**References**

1. Meltzer, M, and Franklin, EC: Cryoglobulins, rheumatoid factors and connective tissue disorders. *Arthritis Rheum* 10:489-92, Oct 1967

2. Meltzer, M, et al: Cryoglobulinemia - A study of twenty-nine patients. *Amer J Med* 40:828-56, June 1966

3. Mathison, DA, et al: Purpura, arthralgia, and IgM-IgG cryoglobulinemia with rheumatoid factor activity, *Ann Intern Med* 74:383-90, 1971

4. Barnett, EV, et al: Cryoglobulinemia and disease, *Ann Intern Med* 73:95-107, 1970

5. Zinneman, HH, et al: On the nature of cryoglobulins. *J Immun* 100:594-603, 1968

6. Franklin, EC: Medical grand rounds - cryoglobulinemia. *Amer J Med Sci* 262:50-7, Jul 1971

7. Lapes, MJ, et al: Arthralgia-purpura-weakness-cryoglobulinemia. *Arch Intern Med* 126:287-9, Aug 1970

8. Whitsed, HM, et al: IGA/IgG cryolobulinemia with vaculitis. *Clin Exp Immun* 9:183-91, 1971

9. Cream, JJ: Immunofluorescent studies of the skin in cryoglobulinemic vasculitis. *Brit J Derm* 84:48-53, 1971

10. Porush, JG, et al: Paraproteinemia and cryoglobulinemia associated with atypical glomerulonephritis and the nephrotic syndrome, *Amer J Med* 47:957-66, Dec 1969

11. Wintrobe, MM, and Buell, MV: Hyperproteinemia associated with multiple myeloma. *Bull Johns Hopkins Hospital* 52:156, 1933

12. Lerner, AB, and Watson, CJ: Studies of cryoglobulins. 1. Unusual purpura associated with the presence of a high concentration of cryoglobulin (cold precipitatable serum globulin). *Amer J Med Sci* 214:410, 1947

13. Foley, JF, Karlen, M, and Watson, CJ: Anticoagulant therapy of cryoglobulinemic ulcers in a case of Sjorgen's syndrome. *Jama* 176:149-52, 1961

14. Domz, LA, and Feigin EU: Cryoglobulinemia. Rationale and results of dishydiodxycoumarin (Dicumeral) therapy. *Arch Intern Med* 100:471-3, 1957

15. Meltzer, M, Franklin EC, Elias K et al: Cryoglobulinemia. A clinical and laboratory study II. Cryoglobulins with rheumatoid factor activity. *Amer J Med* 40:837-56, 1966

16. Golde, D and Epstein, W: Mixed cryoglobulins and glomerulonephritis. *Ann Intern Med* 69:1221-7, 1968